

## Hormone Therapy in Menopause Called Safer if Early

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BETHESDA, Md., April 4 -- Coronary heart disease risk in postmenopausal women taking hormone replacement therapy may be a matter of timing.



Women who began hormone therapy within 10 years of starting menopause appear to be at a lower risk for coronary heart disease than women who start after a decade suggested investigators from the Women's Health Initiative (WHI) reported in the April 4 issue of *Journal of the American Medical Association*.

This emerged from a secondary analysis of combined data from the two WHI studies, said Jacques E. Rossouw, M.D., of the WHI branch at the National Heart, Lung, and Blood Institute, and colleagues.

The effect of time on coronary heart disease risk was not statistically significant, but the investigators found, as did earlier analyses of the WHI data, that hormone therapy was associated with an increased risk for stroke. That risk was the same regardless of when during menopause the women started taking hormones.

From the standpoint of coronary heart disease risk, there is "some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms, but does not necessarily imply an absence of harm over prolonged periods of hormone use," the authors wrote.

The investigators found that night sweats and hot flashes, two of the most common indications for prescribing hormone replacement therapy, were themselves risk markers for elevated coronary heart disease risk in women on hormone therapy. Dr. Rossouw noted in an interview that a small number of women for whom hot flashes and night sweats are a chronic problem may continue using hormones indefinitely.

"That's the group that has a greater chance of having high blood pressure or diabetes, being overweight, and are at particular risk if they take hormone therapy," he said. "On the other hand, women who start the hormone close to the menopause with those symptoms are not at increased risk for coronary artery disease at the very start."

The WHI was comprised of two randomized controlled trials of hormone therapy. In one trial, 10,739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (Premarin) or placebo.

In the second trial, 16,608 postmenopausal women with intact uteruses were randomized to the same conjugated equine estrogen/medroxyprogesterone acetate or placebo. The trials included women who ranged in age from 50 to 79 at enrollment in 40 U.S. clinical centers from September 1993 to October 1998.

In July 2002 the National Institutes of Health halted the Prempro WHI trial because that combination was associated with a significant increase in the relative risk of breast cancer as well as significant increases in the relative risk of heart attack, stroke and venous thrombosis.

In the current study, "the justification for this analysis is really the intense interest on the part of various groups whether the risk benefit profile might be somewhat different and more favorable for younger, recent menopausal women, who are the women who are making hormone therapy decisions," said co-author Ross L. Prentice, Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle, in an interview.

The primary endpoint was a statistical test for trend of the effect of hormone therapy on coronary heart disease and stroke across categories of age and years since menopause in the combined trials.

They identified 396 cases of coronary heart disease in the hormone-replacement group, compared with 379 cases in controls, and 327 cases of stroke among hormone users, compared with 239 strokes in placebo controls.

The authors found that for women who were less than 10 years out since the start of menopause, the hazard ratio for coronary heart disease was 0.76 (95% confidence interval, 0.50-1.16). For those 10 to 19 years out, the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for those two decades or more out, the hazard ratio was 1.28 (95% CI, 1.03-1.58). But the trend did

not meet the statistical significance test ( $P$  for trend=0.02), the authors noted (the pre-specified level for significance was  $P<0.01$  to account for multiple testing and post-hoc nature of the analysis).

In absolute terms, the excess risk for coronary heart disease for women within 10 years of menopause was -6 per 10,000 person-years, compared with 4 per 10,000 for women 10 to 19 after the start of menopause, and 17 per 10,000 for women 20 years or more away from the beginning of menopause.

Broken down by age, the analysis showed that women in their 50s had a coronary heart disease hazard ratio of 0.93 (95% CI, 0.65-1.33), with an absolute excess risk of -2 per 10,000 person-years. Among women ages 60 to 69 years, the hazard ratio was 0.98 (95% CI, 0.79-1.21), with an absolute excess risk of -1 per 10,000 person-years, and among those who were 70 to 79 years, the hazard ratio was 1.26 (95% CI, 1.00-1.59), with an excess risk of 19 per 10,000 person-years.

But here, too, the differences among age groups was non-significant ( $P$  for trend=0.16).

The analysis also showed that women on hormone therapy had a 32% higher risk of stroke (hazard ratio 1.32, 95% CI, 1.12-1.56), and that the risk did not vary significantly with either age or time since the start of menopause.

### **Action Points**

Explain to patients who ask that it is currently recommended that hormone therapy in women during menopause be restricted to short-term use for control of severe symptoms such as hot flashes and night sweats.

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